PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Applicant:	Serge Louis Boulet et al.	Group Art Unit: 1626
Serial No.:	10/597,835	Examiner: Sun Jae Y Loewe
Application Date:	February 18, 2005	Conf No.: 6937
US Nat'l Entry Date (if applicable):	August 9, 2006	
For:	PHARMACEUTICAL COMPOUNDS	
Docket No.:	X-16288	

SUBMISSION UNDER 37 C.F.R. 1.114

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
Sir:

Applicants submit a request for continued examination (RCE) under 37 C.F.R. 1.114 contained herewith.

Applicants submit for convenience a copy of the IDS form, scientific article (Beaton, H; *et al.*; *Biorganic & Medicinal Chemistry Letters*, 11 (2001) pages 1023 – 1026) and Information Disclosure Statement Letter submitted and entered September 11, 2008 but not considered under 37 C.F.R. 41.33.

Applicants request non-entry of the unentered claim amendments submitted after final rejection and received July 11, 2008.

Applicants submit the below arguments under 37 C.F.R. 1.114.

Claim Rejections under 35 USC 103(a)

In the Office Action dated April 11, 2008, the Examiner made final the rejection of Claims 1, 6, 8, 15 and 33 as obvious under 35 USC 103(a) based on examination of the elected species, Example 30, in view of Cheshire *et al.*. The examiner discusses the teaching/suggestion/motivation to make changes to a specific compound disclosed Cheshire *et al.*

to arrive at Applicant's elected species. In this action, the Examiner refers to the Graham v. Deere analysis and summary presented in the office action dated September 5, 2007:

> "One of ordinary skill would be motivated to make the modification required to arrive at the instant invention with reasonable expectation of obtaining a compound that is an inhibitor of nitric oxide synthase. The motivation would be to make alternate compounds that are inhibitors of nitric oxide synthase."

Applicants maintain the assertion that neither the claimed invention nor the elected species of Example 30 are obvious in view of Cheshire *et al.* To establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. MPEP §2143.

Applicants respectively submit that one skilled in the art of medicinal chemistry of nitric oxide synthase (NOS) inhibitors with the knowledge available in Beaton, H; *et al.*; *Biorganic & Medicinal Chemistry Letters*, 11 (2001) pages 1023 – 1026 would not be motivated to start with the compound of Cheshire *et al.* to arrive at compounds of the current invention as inhibitors of nitric oxide synthase. Applicants further submit even if a skilled artisan would be motivated to start with the compound of Cheshire *et al.,* in view Beaton *et al.*, there would be no reasonable expectation that the structural modification employed would produce an inhibitor of nitric oxide synthase.

No motivation to start with the prior art compound of Cheshire *et al.* to make new inhibitors of nitric oxide synthase in view of Beaton *et al.*

Applicants assert, in view of Beaton *et al.,* there is no suggestion or motivation. to start with the 5-substituent of the phenoxypropylamines of Cheshire *et al.* to arrive at the 4-substituted compound of the elected species Example 30 as a inhibitor of nitric oxide synthase.

Beaton *et al.* teaches the desirability of compounds which are selective in inhibiting a specific NOS enzyme, the isoform iNOS. Compounds which are non-selective have demonstrated undesirable cardiovascular side effects arising from inhibition of the isoform eNOS (see page 1023). A skilled artisan seeking to make alternate compounds that are inhibitors of nitric oxide synthase would be motivated to make compounds which lack undesirable eNOS activity. Even though Cheshire *et al.* discloses certain of phenoxypropylamines which are

inhibitors of nitric oxide synthase particularly iNOS, it makes no teaching as to which compounds may or may not inhibit eNOS activity nor does it teach the desirability of compounds which lack eNOS activity. Thus, a skilled artisan seeking to make alternate compounds that are inhibitors of nitric oxide synthase would be motivated to make compounds which are selective inhibitors that lack eNOS activity and would not start with the non-selective phenoxypropylamines of Cheshire *et al.* which are disclosed as inhibitors of nitric oxide synthase including the undesirable isoform eNOS.

In the quest for selective inhibitors, Beaton *et al.* further discloses a series of 3,4-dihydro-1-isoquinolinamines with a wide range of selectivity toward NOS and features the discovery of one of the most selective inhibitors known at that time, compound **5j**. Compound **5j** is shown to be a potent inhibitor of iNOS with no significant activity toward eNOS (see pages 1023-1024). A skilled artisan seeking to make alternate compounds that are inhibitors of nitric oxide synthase would be motivated to start with a selective iNOS inhibitor such as compound **5j** of Beaton *et al.*, and not a phenoxypropylamine of Cheshire *et al.* to arrive at compounds that lack eNOS activity.

No reasonable expectation that making a positional isomer of the compound disclosed in Cheshire *et al.* would lead to an inhibitor of nitric oxide synthase

Applicants assert in view of Beaton *et al.,* even if a skilled artisan would be motivated to start with a compound of Cheshire *et al.,* there would be no reasonable expectation that making a positional isomer modification would produce an inhibitor of nitric oxide synthase.

In exploring structural variation of the 3,4-dihydro-1-isoquinolinamines, Beaton *et al.* highlights the dramatic effects of positional isomer change on the inhibition of nitric oxide synthase. In particular, making one change in the position of a fluorine substituent, in this case from the 5 to the 6 position, has little effect in that it maintains activity, while moving the same substituent one additional position, from the 6 to the 7 position, produces a compound which is essentially inactive (see Beaton *et al.* page 1024 Table 1). The following is a quotation from the Results and Discussion section on page 1024 (emphasis added):

> "Whilst fluorine substitution meta or para in the phenyl substituent or at positions 5 or 6 in the isoquinoline ring can be made with little or no effect on either the potency or selectivity profile of the compounds, dramatic effects occur on substitution at the

isoquinoline 7 or 8 position. While the former is almost inactive, the latter results in a 34-fold increase in iNOS activity…"

These dramatic effects demonstrate the unpredictably of positional isomer changes in the medicinal chemistry of nitric oxide synthase inhibitors. Thus, a skilled artisan seeking to make alternate compounds that are inhibitors of nitric oxide synthase would not have a reasonable expectation that making a positional isomer of the compound disclosed in Cheshire *et al.* would lead to an inhibitor of nitric oxide synthase.

In view of the above arguments and additional evidence, Applicants assert that the instantly claimed compounds are not obvious in view of Cheshire *et al.* under 35 U.S.C. 103(a). Applicants respectively request allowance of Claims 1, 6, 8, 15 and 33.

Applicants respectfully request consideration of the submission under 37 C.F.R. 1.114 and reconsideration and withdrawal of the rejection. Allowance of Claims 1, 6, 8, 15 and 33 is kindly solicited. The Examiner is invited to contact the undersigned agent should any questions arise as a result of the submission provided herein.

Respectfully submitted,

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